Epidemiol. Infect. (2001), **126**, 365–372. Printed in the United Kingdom

Acute poststreptococcal glomerulonephritis: public health implications of recent clusters in New South Wales and epidemiology of hospital admissions

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(*Accepted 20 January 2001*)

SUMMARY

Acute poststreptococcal glomerulonephritis (APSGN) is an inflammatory kidney condition that can complicate Group A streptococcal infections. Two clusters of APSGN occurred recently in New South Wales (NSW), Australia; one in a rural town in December 1999 and the other in a Sydney suburb in January 2000. We interviewed carers of the affected children but found no common exposures except three of the Sydney cases were cousins in frequent contact. To assess the probability of these clusters occurring, we analysed hospital admissions for acute glomerulonephritis, as a proxy for APSGN in younger patients. The incidence of acute glomerulonephritis in NSW during 1989/90–1997/8 in residents aged under 20 years was 2·2/100000/year (95% CI 2·0–2·5). Incidence was highest in children aged 5–9 years, boys and Aboriginal children. We found no evidence for other clusters during that period. The recent clusters highlight the continued potential for unexpected future outbreaks of APSGN.

INTRODUCTION

In late December 1999, a general practitioner reported that he had encountered three cases of acute post-reptococcal glomerulonephritis (APSGN) in the preceding 2 months in the same small rural town (population approximately 2000) in the central west of New South Wales (NSW), Australia. Subsequently, in late January 2000, three more cases were reported, this time in a single suburb in central Sydney. A subclinical case was subsequently identified in the same suburb.

Infections of the skin or throat by *Streptococcus pyogenes* (Group A streptococcus) bacteria are common and generally uncomplicated but can sometimes lead to potentially serious immune response-based complications including rheumatic fever and APSGN [1]. In developed countries, such complications were common up to the middle of the 20th century, but now occur less frequently. However, they are still relatively common in developing countries or communities that experience overcrowding, poor housing and poor hygiene [1, 2]. In Australia, rates are particularly high in Aboriginal communities in the far north of Australia [3, 4]. Recent evidence of an increase in severe suppurative and immune-based complications of streptococcal infections in developed countries has led to growing concern about a re-emergence of more severe Group A streptococcal infections around the world [1, 2, 5].

APSGN is one of several forms of acute glomerulonephritis, which is a disease in which the glomeruli of the kidneys become inflamed, permitting

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blood and proteins to permeate into the urine. The process by which the glomeruli become injured during streptococcal infection is uncertain, but is believed to be related to the body's immune response to the invading organism. Presenting symptoms are typical of any form of acute nephritic syndrome: haematuria, proteinuria, oliguria, oedema, hypertension and acute renal failure. APSGN can be distinguished from other forms of glomerulonephritis by evidence of recent Group A streptococcal infection through serological markers of streptococcal infection, and low serum C3 complement. Prognosis is generally good, with most patients recovering completely with only supportive therapy [6,7].

The epidemiology of APSGN in a modern, developed setting is unclear from the literature, and we were unable to find reports of the incidence of this condition in the general Australian population. Further, APSGN is not a notifiable disease in NSW. Therefore, to determine whether these clusters were unusual in NSW, we utilized hospital admission data as the best available source for describing the recent epidemiology of APSGN in NSW.

Table 1. *Case definition for acute poststreptococcal glomerulonephritis*

Case definition

All four of the following criteria are required for a clinical case. For a sub-clinical case, only criteria 2, 3 and 4 are required.

1. *Clinically compatible illness with one or more of*:
   - Oedema (swelling of the face or limbs).
   - Macroscopic haematuria (visibly dark urine).
   - High blood pressure (diastolic > 80 mmHg if 13 years of age or younger, or > 90 mmHg if older than 13 years).
2. *Microscopic glomerular haematuria*
   - If urine sent to a laboratory for microscopy: red blood cells (RBC) > 10/ml.
   - If urine tested using dipstick urinalysis: haematuria of 2+ or more.
3. *Evidence of recent streptococcal infection*
   - Positive Group A streptococcal culture from skin or throat, or elevated serum antibodies to Group A streptococci; antistreptolysin O (ASO) or anti-deoxyribonuclease B (anti-DNase B).
4. *Reduced serum complement (C3) level*

METHODS

Cluster investigation

In investigating the cases, we adopted the case definition for acute poststreptococcal glomerulonephritis defined in the Northern Territory (Australia) Health Services guidelines for APSGN (Table 1) [8]. Because APSGN can manifest as microscopic haematuria without overt clinical disease [4], a sub-clinical case was defined as criteria 2, 3 and 4 only. Patient information was obtained from the treating medical officers, the patient's parents or guardians, and medical records of the treating hospitals. Pathology results were obtained from medical officers and by directly contacting the relevant pathology laboratories. On 1 January 2000, active surveillance was implemented, with all 17 Area Health Service Public Health Units across NSW being directed to canvas paediatric units of hospitals for further suspected cases.

Analysis of hospital admissions

We used the NSW Inpatient Statistics Collection (ISC) [9] to extract de-identified information on patients aged under 20 years, residing in NSW and discharged from hospital in the period 1 July 1989 to 30 June 1998 with a principal diagnosis of acute glomerulonephritis. Diagnoses in the data base were coded from the patient medical records by hospital Health Information Managers using the International Classification of Diseases, Revision Nine, Clinical Modification (ICD-9-CM) [10]. Acute glomerulonephritis is captured under ICD-9-CM code group 580. Although there is a more specific four digit subcode for acute proliferative glomerulonephritis (580.0) which includes APSGN, we included all admissions for acute glomerulonephritis as a proxy for APSGN. This is because there was a substantial proportion (30%) of acute glomerulonephritis admissions assigned a principal diagnosis of acute glomerulonephritis of unspecified type (580.9), which may have included cases of APSGN. This can arise when a non-specific diagnosis, such as 'acute nephritis' is recorded on the hospital medical record with no indication of the particular type. Further, earlier studies have reported that APSGN accounts for 69–91% of admitted cases of acute glomerulonephritis in children [11–13]. The other four digit sub-codes under 580 are rapidly progressive glomerulonephritis (580.4) and other specified acute glomerulonephritis (580.8), which were included. Nephrotic syndrome (581), chronic glomerulonephritis (582), nephritis and nephropathy not specified as being acute or chronic (583), and acute renal failure

(584) were excluded. The ISC has been fully enumerated since July 1993, and partially enumerated for some hospitals prior to July 1993. A sample weighting factor on the data base [14] was used to estimate total hospitalizations in those hospitals that contributed sampled data prior to this date. However, 99% of the acute glomerulonephritis admissions were to fully enumerated hospitals, and therefore the influence of sampling would be small. Interstate admissions of NSW residents were included.

To better estimate the true population incidence of acute glomerulonephritis leading to hospitalization, we removed obvious multiple admissions of the same person by deleting records with the same age in years (to two decimal places), sex and Statistical Local Area [15] of residence occurring within 60 days of the initial hospitalization. The departure status of each admission episode aided in verifying multiple admissions arising from patient transfers.

Probabilities for counts of hospital admissions for acute glomerulonephritis were calculated assuming a Poisson distribution of the admissions over time; for all NSW the frequency distribution of admissions per month was not significantly different from a theoretical Poisson distribution with the same average frequency (goodness of fit: $\chi^2 = 0{\cdot}16$, $P = 1{\cdot}0$). The confidence intervals of crude admission rates were calculated using the exact method for the Poisson distribution. Confidence intervals for proportions were calculated using the exact method for the binomial distribution [16]. Analysis was performed using SAS statistical software [17].

Knox's method was applied to the hospital admission data to assess the tendency of acute glomerulonephritis in NSW to cluster in time and space (geographically) [16]. The method involves a pair-wise comparison of each event with every other event to determine whether each pair is adjacent in time and/or space. In our analysis, adjacent in time was defined as two admissions occurring 31 days or less apart, and adjacent in space was defined as two admissions occurring in residents of the same Statistical Local Area.

RESULTS

Cluster investigation

The rural cluster consisted of two girls and a younger boy aged 5–19 years and living in the same rural town. All three reported preceding throat symptoms, and none had evidence of skin sores. None of these cases were related, or had any apparent common exposure, except that the two younger children attended the same school and had been swimming at the same local pool during the week preceding their throat symptoms. They had no contact with each other at school. One child was admitted to hospital and the others were treated in the outpatient department (Table 2).

In Sydney, the cluster involved four boys aged under 10 years living in the same suburb, three of whom were cousins and of Polynesian background. The first boy hospitalized was unrelated to the three cousins, attended a different school and had no apparent common exposure. The three cousins each lived in separate households but played together regularly. Only one of the Sydney cases had evidence of a throat infection (peritonsillar abscess). The first boy hospitalized had a preceding purulent lesion on his arm. The three cousins had evidence of possible skin infection related to insect bites or superficial injury (Table 2). One case was subclinical.

Hospital admissions

There were 347 admissions for acute glomerulonephritis in patients aged under 20 years between July 1989 and June 1998. Males comprised two-thirds of the admissions in the period. Admissions were concentrated in patients aged 5–9 years ($n = 149$, 43%) (Table 3), and peaked at age 7 years ($n = 39$, 11%). The number of admissions declined from 47 in 1989/90 to 35 in 1990/1, increased to 53 in 1992/3 and then declined steadily to 20 admissions in 1997/8 (Table 3). Eight percent (95% CI 5–11%) of admissions were of people identified as being of Aboriginal or Torres Strait Islander origin (Table 3). This compares with only 3% of the total NSW population aged under 20 years identifying as being of Aboriginal or Torres Strait Islander origin in the 1996 Australian census [18]. The principal diagnosis was proliferative glomerulonephritis (which includes APSGN) in two-thirds and unspecified glomerulonephritis in almost one-third of the admissions in this age group (Table 3).

Admissions for acute glomerulonephritis occurred at an average annual rate of 2·2 (95% CI 2·0–2·5) per 100000 residents aged under 20 years across NSW over the 9-year period to June 1998. The rates in the regions in which the clusters occurred were unremarkable (the rural region; Macquarie Health Area:

Table 2. *Description of cases of acute poststreptococcal glomerulonephritis according to the case definition applied*

				Clinically compatible illness			Microscopic haematuria	Recent streptococcal infection?					
Area Health Service and case no.	Age group (years)	Sex	Date of onset of APSGN	Oedema	Visibly dark urine	Diastolic BP on admission (normally $\leqslant$ 80)	Red blood cells (no. $\times 10^6$/ml) (normally $<$ 10)	Characteristics and date of onset	Skin swab	Throat swab	ASO serology (IU/ml) (normally $<$ 200*)	Anti-DNase B serology (normally $<$ 170)	Serum C3 complement (g/l) (normally 0·83–1·70)
Macquarie													
1	10–14	F	5 Nov 1999	No	Yes	80	10–100	Throat infection 31 Oct 1999	n.d.	n.d.	426 (24/11/99); 397 (05/12/99)	200	n.s.a.
2	15–19	F	10 Dec 1999	Yes	Yes	85	10–100	Throat infection 23 Nov 1999	n.d.	n.d.	858	n.d.	n.s.a.
3	5–9	M	13 Dec 1999	Yes	Yes	80	$>$ 100 (14/12/99); $>$ 100 (23/12/99)	Throat infection 24 Nov 1999	n.d.	n.d.	4449 (14/12/99); 4864 (20/12/99)	$>$ 1600	n.s.a.
Central Sydney													
1	5–9	M	8 Jan 2000	Yes	Yes	87	$>$ 100	Purulent arm lesion 25 Jan 1999	n.d.	−ve	300	680 (12/1/00); 320 (13/1/00)	0·21
2	5–9	M	16 Jan 2000	Yes	Yes	90	$>$ 100	Dry knee wound/ insect bites 1 Jan 2000	n.d.	−ve	200	680	0·16
3	5–9	M	26 Jan 2000	Yes	Yes	80	$>$ 100	Peritonsillar abscess 17 Jan 200.	n.d.	−ve	100 (26/1/00); $<$ 100 (24/1/00)	680	0·56 (25/1/00); 0·45 (24/1/00)
4	0–4	M	Asymptomatic	No	No	71	11–100 (29/1/00); $>$ 100 (31/1/00)	Insect bites 1 Jan 2000. Became wet itchy sores	n.d.	−ve	$<$ 100	$\geqslant$ 1360	0·39

BP, blood pressure; −ve, no pathogens found; n.d., not done; n.s.a., no serum available; ASO, antistreptolysin O antibody to Group A streptococci titre; anti-DNase B, anti-deoxyribonuclease B antibody to Group A streptococci titre.
*ASO titres may be 200 or more in healthy, school-age children.

Table 3. *Characteristics of admissions (n = 347) for acute glomerulonephritis in patients aged under 20 years between July 1989 and June 1998 in NSW*

Characteristic/category	No.	% (95% CI)
Age (years)		
0–4	63	18·2 (14·2–22·6)
5–9	149	42·9 (37·7–48·3)
10–14	78	22·5 (18·2–27·2)
15–19	57	16·4 (12·7–20·8)
Sex		
Male	225	64·8 (59·6–69·9)
Female	122	35·2 (30·1–40·4)
Aboriginality		
Non-Aboriginal	298	85·9 (81·8–89·4)
Aboriginal/Torres Strait Islander	28	8·1 (5·4–11·5)
Not stated/missing	22	6·3 (4·0–9·4)
Year of admission		
1989/90	47	13·5 (10·1–17·6)
1990/1	35	10·1 (7·1–13·7)
1991/2	42	12·1 (8·9–16·0)
1992/3	53	15·3 (11·7–19·5)
1993/4	48	13·8 (10·4–17·9)
1994/5	41	11·8 (8·6–15·7)
1995/6	32	9·2 (6·4–12·8)
1996/7	29	8·4 (5·7–11·8)
1997/8	20	5·8 (3·6–8·8)
Type of acute glomerulonephritis		
Proliferative (including APSGN)	227	65·4 (60·2–70·4)
Rapidly progressive	3	0·9 (0·2–2·5)
Other specified	14	4·0 (2·2–6·7)
Unspecified	103	29·7 (24·9–34·8)
Total	347	100·0

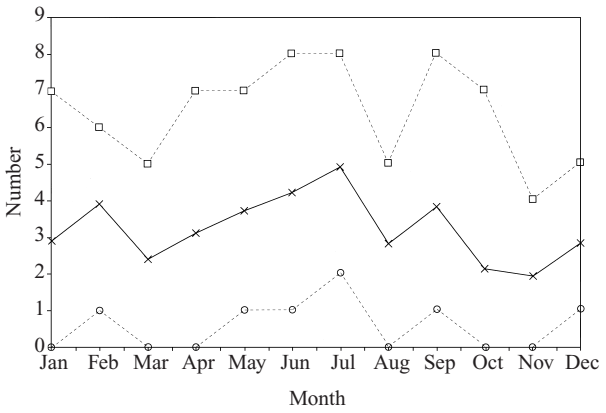

Fig. 1. Average, minimum and maximum number of admissions for acute poststreptococcal glomerulonephritis in each month from July 1989 to June 1998 in persons aged under 20 years in NSW. ○, minimum; ×, average; □, maximum.

3·2/100000, 95% CI 1·5–5·9; inner Sydney; Central Sydney Health Area: 2·3/100000, 95% CI 1·4–3·5). There was no seasonal pattern of admissions evident in NSW over the 9 years, with an average of between 2 and 5 admissions occurring in each month. There was a maximum of 7 admissions occurring in any January over the period, and a maximum of 5 in any December (Fig. 1).

The clustering of cases in Sydney in January was highly unusual; the mean number of admissions in January of residents of the inner Sydney region (Central Sydney Health Area) aged under 20 years over the 9-year period was 0·22 (95% CI 0·0–0·8). Using the mean and its confidence limits as the parameters of Poisson distributions, the probability of three or more admissions in January in inner Sydney was 0·002, with a range of 0·000–0·047. With only one of the three cases from the rural cluster being admitted, we were unable to determine from hospital

admission data whether the observed cluster in that area was unusual, although we are unaware of other such clusters of non-hospitalized cases occurring in NSW. For residents aged under 20 years of the central western region of NSW (Macquarie Health Area), the mean number of admissions in December over the period was 0·37 (95% CI 0·09–1·04). The probability of one or more admissions in the central west in December was then 0·309 (0·086–0·647).

The hospital admission data did not reveal a tendency to cluster in time and space. Over the 9 years, there were 18 pairs of patients living in the same Statistical Local Area and admitted within 31 days of each other, compared with 19·4 expected pairs using Knox's method. The probability of 18 or more pairs occurring was 0·66.

DISCUSSION

We identified two clusters of acute glomerulonephritis occurring around the same time but in geographically distinct parts of NSW. The first, in late 1999, occurred in a small rural town and involved three unrelated children of Caucasian origin with no apparent common exposure. The second, in early 2000, occurred in an inner Sydney suburb, and involved three related children of Polynesian origin who played together regularly and who therefore were likely to have a high chance of a common exposure. A fourth, Caucasian, child in the same suburb was also affected, but we could find no common exposure.

Analysis of hospital admission data for NSW for the 9 years to June 1998 revealed that admissions for acute glomerulonephritis occurred more commonly in boys, in Aboriginal children, and around the age of 7 years. There was a declining trend in admissions in each year since a peak in 1992/3 and no strong seasonal pattern was evident, contrary to the New Zealand experience where a distinct seasonal peak in admissions occurs between April and June [19]. Based on expected counts of admissions in the areas affected, we were able to determine that the recent cluster of four patients with APSGN from one suburb in Sydney was a highly unusual event. With only one of the recent rural cases being admitted, we could not determine from the hospital admissions data whether that cluster was unusual. However, analysis of statewide admissions data did not reveal any tendency for acute glomerulonephritis to occur in clusters during 1989–98.

In the absence of literature describing the epidemiology of APSGN in modern developed settings, the hospital admissions data provided a readily available means by which to describe quickly its epidemiology in NSW. The data have some limitations, however. First, we were unable to determine the epidemiology of non-admitted cases. Second, hospital medical records are often incomplete or unclear [20], possibly explaining why the specific type of acute glomerulonephritis was not coded for almost one-third of the admissions. We therefore had to analyse all admissions coded as acute glomerulonephritis as a proxy for APSGN. However, proliferative glomerulonephritis, which includes APSGN, accounted for two-thirds of the admissions. Finally, the indigenous status of admitted patients is almost certainly under-reported in NSW [21].

Attack rates of glomerulonephritis following Group A streptococcal infection vary by the ability of a particular strain of the bacteria to cause glomerulonephritis (nephritogenic). Attack rates from nephritogenic strains of 5–43% have been reported, depending on strain, age and site of infection [22]. A population-based study reported an attack rate of 0·7% following streptococcal pyoderma in African-American children aged 2–6 years living in rural United States of America [23]. In the first half of the twentieth century, when APSGN was more common in developed countries, outbreaks of the disease demonstrated a variety of epidemiological manifestations: sporadic instances, geographically localized clusters, clusters within families and widespread epidemics [24]. The pronounced variability in attack rates and in the prominence of particular strains of Group A streptococci over time [25] highlight the unpredictable nature of these infectious agents and the potential for further clusters of APSGN to occur in future in NSW.

At present, prophylactic antibiotic use is the only available means of controlling Group A streptococcal infection. Whether antibiotic treatment is protective against progression to glomerulonephritis following streptococcal infection is unclear, with contradictory results reported in the literature [26, 27]. However, a recent systematic review and meta-analysis of trials of antibiotic treatment following sore throat showed a trend towards being protective against glomerulonephritis [28].

The Northern Territory of Australia has evidence-based [29] recommendations for community-wide prophylactic antibiotic use when clusters of APSGN occur in isolated Aboriginal communities [8], a setting

prone to epidemics probably due to high background rates of streptococcal skin infections. Should prophylactic antibiotics be recommended to prevent the spread of APSGN when clusters occur in modern developed urban and rural settings? Unlike the far north of Australia, clusters of more than two cases of APSGN are rare in both urban and rural NSW. Furthermore, there is no evidence that further intervention in relation to the clusters we described would have affected further spread of APSGN. We therefore make the following recommendations for the public health response to clusters of APSGN in modern developed settings such as NSW: household contacts with overt throat or skin infection should be treated with oral antibiotics (generally penicillin); families of cases should be educated to seek medical advice if signs or symptoms of throat or skin infection or acute glomerulonephritis occur; clinicians should report clusters to Public Health Units who can investigate for common exposures to exclude possible point sources of infection. Where ongoing risk is identified, additional control measures may be required.

ACKNOWLEDGEMENTS

The authors would like to thank the members of the NSW Infectious Disease Advisory Committee for their assistance in developing the recommendations. We would also like to thank staff of the Institute for Clinical Pathology and Microbiological Research, the Royal Prince Alfred Hospital, Concord Repatriation Hospital, Sydney Children's Hospital and the New Children's Hospital pathology laboratories for their assistance. Dr Fay Johnston of Territory Health Services provided valuable advice.

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